Abbreviated Title: Avelumab for RRP

NIH Protocol #: 16C0160

NCT #: NCT02859454

Version Date: 12/1/2020

Title: A Phase II Study of Avelumab in Subjects with Recurrent Respiratory Papillomatosis

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Investigational Agent:

Drug Name:	Avelumab
IND Number:	130884
Sponsor:	Center for Cancer Research
Manufacturer:	EMD Serono

Commercial Agents: None

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PRÉCIS

Background

- Recurrent respiratory papillomatosis (RRP) is a rare papillomatous disease of the aerodigestive tract that is caused by the Human Papilloma Virus (HPV).
- RRP can progress to cause airway compromise, fatal pulmonary lesions, and invasive cancers.
- There is no effective systemic therapy for RRP. Patients require repeated interventional procedures for disease control.
- Study of a small number of RRP samples has shown PD-L1 expression by inflammatory mononuclear cells and by papilloma epithelial cells.
- This clinical trial will evaluate the activity of a PD-L1-targeted drug, avelumab, in the treatment of RRP. This drug was selected for its demonstrated activity in a variety of cancers and for its acceptable safety profile.

Objective

- Determine the complete response rate for avelumab in the treatment of patients with RRP.

Eligibility

- Histologically confirmed diagnosis of RRP.
- One of the following:
    - A Derkay anatomic score of 10 or greater and a history of two or more endoscopic interventions in the last 12 months for control of RRP.
    - Pulmonary RRP with pulmonary disease that is measurable by computed tomography scan.
    - Tracheal involvement with RRP that has required either two or more endoscopic interventions in the last 12 months or a tracheostomy.
- Age 18 years or greater.
- Eastern Oncology Cooperative Group Performance Score of 0 or 1.

Design

- Phase II clinical trial
- Simon optimal two-stage design with initial enrollment of 12 patients and expansion to 37 patients if one or more complete response(s) is/are observed in the initial patients.

Robbins Y, *et al. J Immunother Cancer* 2021; 9:e003113. doi: 10.1136/jitc-2021-003113

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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

To determine the complete response rate for avelumab in the treatment of patients with recurrent respiratory papillomatosis (RRP).

1.1.2 Secondary Objectives

- Exploratory analyses to assess:
    - PD-L1 expression as a potential biomarker of response.
    - HPV type as a potential biomarker of response.
    - Induction of HPV-specific T cells responses.
    - Clearance of HPV infection from normal appearing mucosa.
- Determine the effect of treatment with avelumab on Derkay and Voice Handicap Index-10 scores.
- Determine the partial response rate for avelumab
- Determine the duration of clinical responses to avelumab

1.2 BACKGROUND AND RATIONALE

1.2.1 Recurrent respiratory papillomatosis (RRP)

RRP is a rare but difficult-to-treat and sometimes fatal neoplastic disease of the aerodigestive tract. RRP is caused by infection with human papillomavirus (HPV) type 6 or 11, or more rarely type 16 [1]. Approximately 1,500 new cases of RRP are diagnosed each year in the United States [2]. RRP is classified based on age of onset as juvenile or adult. Juvenile-onset disease has an incidence of 4/100,000 and tends to have an aggressive clinical course. Adult-onset RRP has an incidence of 2-3/100,000 and tends to have a more indolent clinical course. RRP morbidity and mortality results from papilloma mass effects on the vocal cords, airways, or lungs. This may cause voice changes, stridor, airway occlusion, loss of lung volume, and/or pneumonia [3]. Repeated procedures are required to debulk and monitor the disease, which exposes patients to anesthetic and surgical risk, and emotional distress. It is estimated that the economic cost of RRP is $150M in the United States each year [2]. Although rare (one to three percent of cases) RRP can transform into invasive squamous cell carcinoma [4]. Subsequent mortality is based upon the clinical stage of the malignancy at the time of diagnosis.

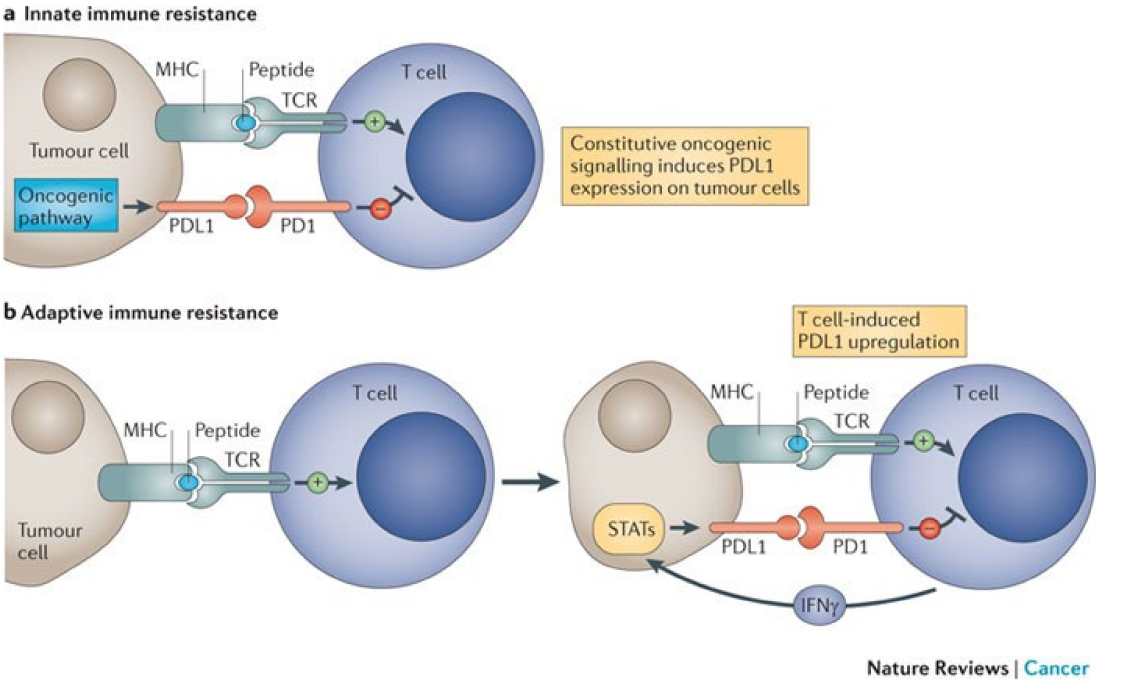
There is no cure for RRP. The mainstay of treatment is endoscopic debulking with ablation or excision of papillomatous lesions. Surgical principles dictate that, to minimize morbidity from treatment, papillomatous disease but not normal appearing epithelium is removed. It is thought that latent HPV viral particles persistent in an inactive state in the clinically-normal mucosa and subsequently become reactivated leading to RRP recurrence [5]. Patients with juvenile-onset RRP require on average 20 surgeries over their lifetime to control their disease [6]. Patients with adult-onset RRP generally require fewer interventions; nonetheless greater than 50% will require 5 or more procedures to control symptoms [7]. Adjuvant systemic therapies have been tested in clinical trials, including systemic interferon-α and local injection of anti-viral and antiangiogenic

agents [5]. Study results have been inconsistent, and no single adjuvant approach has been widely adopted or accepted as the standard of care.

1.2.2 Avelumab

Avelumab is a fully human monoclonal antibody (HuMAb; immunoglobulin G1 [IgG1]) that targets programmed death-ligand 1 (PD-L1). Programmed death-1 (PD-1) is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligand, PD-L1, results in the down-regulation of lymphocyte activation (**Figure 1**). Inhibition of the interaction between PD-1 and PD-L1 promotes activation of adaptive immunity and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Avelumab is produced using standard mammalian cell cultivation and chromatographic purification technologies.

Figure 1



Pardoll, Nat Rev Cancer, 2012

The clinical use of monoclonal antibodies that block T-cell inhibitory receptors has provided transformative information on the nature of the immune system and cancer. An emerging picture suggests that endogenous immune responses can mediate effective tumor regression and/or improved survival even in patients with large volume tumors resistant to other forms of therapy. Some of the unique features of this type of therapy, based largely on experience in advanced melanoma, include: improved overall survival (OS) with or without radiographic responses or improved progression-free survival (PFS); responses that may be delayed or occur after radiographic disease progression; combinations of immune modulators with enhanced or novel activities (in the example of anti-CTLA4 and anti-PD-1 agents); and toxicity that is almost exclusively immune or inflammatory in nature. It is not yet clear what factors determine

responses and which components of the immune system are needed for this to occur. It seems likely that both memory helper and effector cells would be needed to sustain long-term responses. Increasing emphasis has been placed on understanding the relationships of the tumor, cellular infiltrate, and immunologic milieu surrounding each tumor.

PD-1, a 55-kDa type 1 transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that include Ig super family member CD28, CTLA-4, inducible co-stimulator (ICOS), and B and T lymphocyte attenuator (BTLA).[8] PD-1 is transiently but highly expressed on activated T cells functioning to limit immune effectors at the site of activation. Chronic stimulation may prevent the re-methylation of the PD-1 gene leading to continuous expression and characterizes a state of "exhausted" T cells that lose function and proliferative capacity while enhancing a suppressive tumor microenvironment. PD-1 may act together with other T-cell modulating molecules, including CTLA-4, TIM-3, lymphocyte-activation gene 3 (LAG-3) as well as indoleamine-pyrrole 2,3-dioxygenase 1 (IDO-1), cytokines, and transforming growth factor beta (TGF-beta).

Two ligands specific for PD-1 have been identified: PD-ligand 1 (PD-L1, also known as B7-H1 or CD274, expressed on tumor, antigen-presenting cells [APCs], and dendritic cells [DCs]) and PD-L2 (also known as B7-DC or CD273, expressed on endothelial cells). The interaction of PD-1 with PD-L1 and PD-L2 results in negative regulatory stimuli that down-modulate the activated T-cell immune response through SHP-1 phosphatase.

PD-1 knockout mice develop strain-specific lupus-like glomerulonephritis (C57BL/6) and cardiomyopathy (BALB/c). In transplantable tumor models that expressed PD-1 and LAG-3 on tumor-infiltrating $CD4^+$ and $CD8^+$ T cells dual anti-LAG-3/anti-PD-1 antibody treatment cured most mice of established tumors that were largely resistant to single antibody treatment.[9] Despite minimal immunopathologic sequelae in PD-1 and LAG-3 single knockout mice, dual knockout mice abrogated self-tolerance with resultant autoimmune infiltrates in multiple organs, leading to eventual lethality.

PD-L1 expression is found on a number of tumors, and is associated with poor prognoses based on OS in many tumors, including melanoma,[10] renal,[11-13] bladder, esophageal,[14] gastric,[15] ovarian,[16] pancreatic,[17] lung,[18] and other cancers.[8]

The PD-1/PD-L1 axis plays a role in human infections, particularly in hepatitis C virus (HCV) and human immunodeficiency virus (HIV). In these cases, high expression levels of PD-1 were found in viral-specific $CD8^+$ T cells that also display a non-responsive or exhausted phenotype. Non-responsive PD-1-high T cells were observed in simian immunodeficiency virus (SIV) infection in rhesus macaques. Treatment of SIV-infected macaques with an anti-PD-1 mAb (3 mg/kg x4) resulted in decreased viral loads and increased survival along with expanded T cells with increased T-cell functionality.

1.2.2.1 Nonclinical Development of Avelumab

In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, avelumab alone was well tolerated (change this reference to the avelumab IB)[8]. Avelumab bound specifically to monkey PD-L1 with an affinity constant of 1.1 nM. In monkeys, a no-observed-adverse-effect-level was observed at a dose of avelumab significantly higher (140 mg/ml) than that selected for clinical development (10 mg/ml). Avelumab monotherapy increased survival time in MC38

(colon carcinoma) and PANC02 (pancreas adenocarcinoma) tumor-bearing mice in a CD8 T-cell dependent fashion and appeared to induce NK-cell mediated antibody dependent cellular cytotoxicity in some tumors.

1.2.2.2 Clinical Development of avelumab

Avelumab is an investigational fully-human monoclonal antibody (IgG1) that specifically targets PD-L1. It has demonstrated clinical activity in a variety of solid tumor types including NSCLC, merkel-cell carcinoma, gastric, ovarian and bladder cancer. Similar to other checkpoint inhibitors, many responses have been durable lasting beyond the duration of active therapy. Over 700 patients have been treated in initial MTD and expansion cohort phase I trials, with a phase II trial in metastatic merkel-cell carcinoma and a phase III trial in recurrent NSCLC underway. The clinical activity and safety information presented here focuses primarily on data obtained from EMR100070-001 (Phase I, open label trial in primarily Caucasian patients) and MER100070-002 (Phase I, open label trial in Asian patients).

Nine of 53 (16.9%) initial patients experienced ≥ grade 3 AEs potentially related to avelumab including immune-related AEs. None of the subjects treated with doses up to 10 mg/kg experienced a DLT, thus 10 mg/kg q2 weeks dose of avelumab was considered a safe and well-tolerated dose for further investigation in the expansion cohorts

Expansion cohorts in breast, NSCL, gastric, ovarian and urothelial cancer were administered 10 mg/kg every 2 weeks. Of 717 patients treated with this dose and schedule, 498/717 (69%) experienced treatment-related AEs of any grade and 77/717 (10.7%) experienced ≥ grade 3 AEs. The most common grade 3 reactions included infusion side related reactions, (134, 18.7%), fatigue (130, 18.1%), nausea (74, 10.3%), diarrhea (49, 6.8%), chills (48, 6.7%0 and decreased appetite (37, 5.2%). The 14 subjects reporting Grade 4 treatment-related TEAEs included 7 subjects (3.8%) in the NSCLC expansion cohort with the PTs of infusion-related reaction (2 subjects), amylase increased, embolic stroke, frontal lobe epilepsy, monoplegia, syncope, dyspnea, pneumonitis, and autoimmune neutropenia (each in 1 subject). Further Grade 4 treatment-related TEAEs were seen in 5 subjects of the metastatic breast cancer (MBC) expansion cohort (3.0%) with the PTs of gamma-glutamyltransferase increased, hypokalemia, respiratory failure, anemia, neutropenia, thrombocytopenia, and cardiac arrest (each in 1 subject). The other 2 subjects who reported Grade 4 treatment-related TEAEs were 1 subject in the mesothelioma expansion cohort (blood creatine phosphokinase increased) and 1 subject in the urothelial carcinoma expansion cohort (myositis).

The 4 subjects who experienced Grade 5 treatment-related TEAEs were 2 subjects in the NSCLC expansion cohort (radiation pneumonitis [Subject ID 172-0004] and acute respiratory failure [Subject ID: 168-0004]) and 2 subjects in the MBC expansion cohort (respiratory distress [Subject ID 139-0004] and acute hepatic failure [Subject ID: 120-0014]).

The NSCLC and ovarian carcinoma expansion cohorts from the EMR100070-001 trial have demonstrated objective response rates of 13.6% and 10.7%, respectively. Within the NSCLC expansion cohort, progression free survival was extended from 5.9 weeks to 12 weeks and overall survival was extended from 4.6 months to 8.9 months.

1.2.2.3 Pharmacokinetics

Pharmacokinetics (PK) of avelumab was linear in the range of 1 to 20 mg/kg, with dose-proportional increases in maximum serum concentration (C_{max}) and area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), with low to moderate inter-subject variability observed at each dose level (insert avelumab IB here)[8]. Clearance of avelumab is independent of dose in the dose range (1-20 mg/kg). Body weight normalized dosing showed approximately constant trough concentrations over a wide range of body weights. The mean terminal elimination half-life of avelumab is 5 days.

1.2.3 PD-1-targeted therapy for RRP

RRP is caused by HPV infection. HPV infections are common, but most individuals clear the virus without manifesting papillomas, dysplasia, or invasive cancers [19]. Why some immunocompetent individuals are unable to eliminate the virus and therefore develop papillomatosis is not understood. Local therapies fail to eradicate the disease apparently due to chronic persistence of latent virus in normal appearing mucosa. This notion is supported by a study demonstrating the presence of HPV DNA in the clinically healthy mucosa of patients with RRP [20].[21][21][21]. Efforts to study systemic immunotherapy for RRP have been limited. Adjuvant IFN-α after papilloma treatment was shown to increase short-term time to recurrence but did not demonstrate long-term benefit [22].

Clinical trials with new immunotherapeutic agents such as checkpoint inhibitors that block the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), or programmed cell death 1 (PD-1) receptors or their ligands such as PD-L1, have not been reported for the treatment of RRP. PD-1 expression has been observed by flow cytometric analysis of T cells infiltrating respiratory papillomas, and PD-L1 mRNA expression in papillomas has been observed by RT-PCR [23]. Study of a small number of RRP samples by our group has shown PD-L1 expression by inflammatory mononuclear cells and by papilloma epithelial cells (**Table 1** and **Figure 2**). Expression of PD-L1 by tumor-infiltrating immune cells or by the tumor cells themselves has positively correlated with tumor response in clinical trials of drugs PD-1/PD-L1-targeted drugs [24]. This clinical trial will evaluate the activity of a PD-L1-targeted drug, avelumab, in the treatment of RRP. This drug was selected for its demonstrated activity in a variety of cancers and for its acceptable safety profile.

Table 1 PD-L1 expression on RRP

	N (30 samples tested)	%
Epithelial cell membranous or infiltrating hematopoietic cells	24	80
Epithelial cell membranous	18	60
Infiltrating hematopoietic cell	22	73
Epithelial cell membranous and infiltrating hematopoietic cells	16	53

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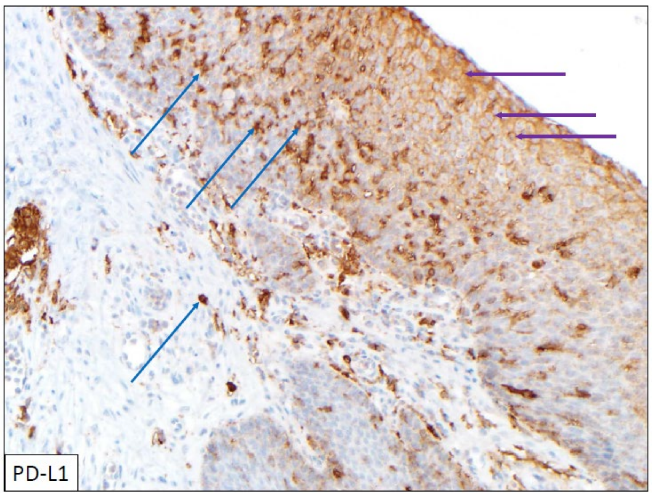
Figure 2



PD-L1 expression by a respiratory papilloma. Blue arrows point to mononuclear inflammatory cells demonstrating strong PD-L1 expression on their surface. Purple arrows point to squamous epithelium of the papilloma with PD-L1 expression. 200x, original magnification.

1.2.4 Summary of risks and potential benefits

This clinical trial is being performed to evaluate avelumab for RRP. Only patients with a substantial disease burden (Derkay anatomic score of 10 or greater) that requires repeated endoscopic interventions (two or more procedures in the last 12 months) will be eligible for treatment. While the vast majority of patients with RRP experience an acceptable level of disease control with infrequent surgical debulking, a small subset of patients have very aggressive disease that requires frequent operative intervention, carries the risk of airway obstruction and the need for a tracheostomy, and affects their voice and breathing to a degree that negatively impacts their quality of life. The inclusion criteria for this study captures these 5-10% of patients most severely affected. Patients with disease that has not met this level of severity will not be subjected to the risks of treatment. The primary protocol risks are the toxicities of avelumab. There may be additional risks of treatment that are specific to RRP such as swelling or progression of papillomas that may lead to worsening symptoms. In addition, there are risks from the general anesthesia and procedures to stage and monitor the disease. General anesthesia will be employed during an initial evaluation to stage the disease, confirm the diagnosis, and debulk papillomas that pose an undue safety risk. It will be used again two weeks after the initiation of treatment at which time the airway will be assessed for safety. A final procedure under anesthesia will be performed at the completion of treatment to remove residual papillomas if they are present. Rare but serious complications can occur with general anesthesia including cardiopulmonary compromise, stroke, and death. In this protocol they are offset substantially by the important safety information related to airway patency, extent of disease, and in some cases surgical removal of disease that is gained by these procedures.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 RRP criteria

- Histological diagnosis of RRP confirmed by pathology report from a CLIA-certified laboratory.
- One of the following:
    - A Derkay anatomic score of 10 or greater (See Section **12.4**) and a history of two or more endoscopic interventions in the last 12 months for control of RRP.
    - Pulmonary RRP with pulmonary disease that is measurable by computed tomography scan.
    - Tracheal involvement with RRP that has required either two or more endoscopic interventions in the last 12 months or a tracheostomy.
- Greater than or equal to 18 years of age.

2.1.1.2 Able to understand and sign the Informed Consent Document.

2.1.1.3 Clinical performance status of ECOG 0 or1. See section **12.1**

2.1.1.4 Willing to undergo endoscopic evaluation with biopsies in compliance with this protocol.

2.1.1.5 No systemic therapy for RRP for four weeks prior to treatment.

2.1.1.6 Screening laboratory values must meet the following criteria and should be obtained within 14 days prior to first dose:

- WBC > 2000/μL
- Neutrophils > 1500/μL
- Platelets > 100 x10^3/μL
- Hemoglobin > 9.0 g/dL
- Serum creatinine < 1.5 x ULN or creatinine clearance (CrCl) > 30 mL/min (measured or calculated using the Cockcroft-Gault formula below):

  Female CrCl: $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$

  Male CrCl: $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$

- AST/ALT ≤ 2.5 x ULN; for subjects with documented metastatic disease to the liver, AST and ALT levels ≤ 5 × ULN
- Total Bilirubin ≤ 1.5 x ULN

2.1.1.7 Sexually active subjects (men and women) and all subjects of reproductive potential must agree to use two methods of contraception: one highly effective and one other effective method for at least 28 days prior, throughout the avelumab treatment and for at least 60 days after avelumab treatment. Highly Effective Methods are defined as: Intrauterine device (IUD), hormonal (birth control pills, injections, implants), tubal ligation and partner's vasectomy; Other Effective Methods are defined as: latex condom, diaphragm and cervical cap.

2.1.1.8 Seronegative for HIV antibody. The experimental treatment being evaluated in this protocol depends on an intact immune system. Patients who are HIV seropositive can have decreased immune function and thus are likely less responsive to the experimental treatment.

2.1.1.9 Seronegative for hepatitis B antigen, positive hepatitis B tests can be further evaluated by confirmatory tests (Hep B DNA Quant, HBV Viral Load), and if confirmatory tests are negative, the patient can be enrolled.

2.1.1.10 Seronegative for hepatitis C antibody unless antigen negative. If hepatitis C antibody test is positive, then patients must be tested for the presence of antigen by Hep C RNA Quant, HCV Viral Load and be HCV RNA negative.

2.1.2 Exclusion criteria

2.1.2.1 Any severe acute or chronic medical or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior, liver disease, lung disease (with the exception of what is specified in inclusion criteria in section **2.1.1.1**) , or laboratory abnormalities that, in the opinion of the investigators, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results and in the judgment of the investigator, would make the patient inappropriate for entry into this study. Patients with mild to moderate asthma or chronic obstructive pulmonary disease (COPD) well controlled with oral or inhaled medications are permitted to enroll.

2.1.2.2 Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, or psoriasis not requiring systemic treatment, are permitted to enroll.

2.1.2.3 Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled, topical intranasal or intro-ocular steroids, and adrenal replacement doses <10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

2.1.2.4 Prior organ transplantation, including allogeneic stem cell transplantation.

2.1.2.5 Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways.

2.1.2.6 Patients who are receiving any other investigational agents

2.1.2.7 Pregnant or breast feeding. Women of childbearing potential must have a negative pregnancy test at screening. Women of childbearing potential include women who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are not postmenopausal. Post-menopause is defined as amenorrhea ≥12 consecutive months. Note: women who have been amenorrheic for 12 or more months are still considered to

be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, anti-estrogens, ovarian suppression or any other reversible reason.

2.1.2.8 History of allergy to study drug components.

2.1.2.9 History of severe hypersensitivity reaction to any monoclonal antibody (Grade ≥ 3 NCI-CTCAE v 4.03), any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma).

2.1.2.10 Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.

2.1.2.11 Persisting toxicity related to prior therapy of Grade >1 NCI-CTCAE v 4.03; however, alopecia, sensory neuropathy Grade ≤ 2 or other Grade ≤ 2 AEs not constituting a safety risk based on investigator's judgment are acceptable.

2.1.2.12 Known alcohol or drug abuse.

2.1.2.13 Vaccination within 4 weeks of the first dose of avelumab and while on trial is prohibited except for administration of inactivated vaccines.

2.2 SCREENING EVALUATION

Study eligibility is based on meeting all of the study inclusion criteria and none of the exclusion criteria at screening before study treatment administration. Screening evaluations may be performed as part of an NIH Screening protocol. This does not include the baseline correlative studies that will only be performed after the patient has signed the consent form for this protocol.

2.2.1 Within 14 days prior to subject enrollment, unless otherwise indicated below:

2.2.1.1 Complete history and physical examination, including ECOG status, weight, vital signs, and oxygen saturation by pulse oximetry at rest and after exertion.

2.2.1.2 Confirmation of the diagnosis of RRP by pathology report from a CLIA-certified laboratory (no time limit).

2.2.1.3 Clinic-based flexible nasopharyngolaryngoscopy and/or tracheoscopy to document disease to the extent that can be evaluated without sedation or general anesthesia. This will include standard bright light endoscopy and may include videostroboscopy. Endoscopy may be omitted in patients with disease that is not endoscopically accessible. This examination will allow determination of a Derkay score that will determine if the patient meets inclusion criteria.

2.2.1.4 Computed tomography scan of the neck and/or chest if patients have known or suspected pulmonary RRP. This examination could also be used to determine if the patient meets inclusion criteria.

2.2.1.5 Hepatitis and HIV testing as detailed in sections **2.1.1.8** - **2.1.1.10** (within 90 days prior to subject enrollment).

2.2.2 Within 3 days prior to subject receiving the first dose of study drug:

2.2.2.1 CBC w/differential, chemistry panel including: LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, glucose, amylase, lipase, TSH, free T4, free T3

2.2.2.2 Pregnancy test in women of childbearing potential.

2.2.2.3 Review of concomitant medications

2.3 BASELINE EVALUATION

After consenting to enrollment in this study, baseline evaluation will include exam under anesthesia (sedation or general anesthesia) including rigid and/or flexible endoscopy to thoroughly assess airway patency and the extent of disease, rule out invasive cancer, debulk lesions that pose a major risk of airway obstruction, and obtain papilloma and normal mucosa tissue for research. Baseline imaging studies will be done if imaging is used for response assessment. For other baseline evaluations please refer to the Study Calendar (Section **3.5**).

2.4 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found here.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

3.1.1 General study plan

This protocol is a phase II study of avelumab. The protocol will enroll subjects with an RRP disease burden that requires repeated surgical procedures for management. Patients with a pathologically confirmed diagnosis of RRP will be screened for this protocol. Patients who appear to be eligible for treatment will be examined via flexible nasopharyngolaryngoscopy and/or tracheoscopy by the Otolaryngology Service. Patients that meet the eligibility criteria will be enrolled onto the study. After enrollment, patients will undergo exam under anesthesia (EUA) staging of RRP with biopsies to confirm baseline staging, debulk disease that poses an impending airway risk and rule out invasive cancer. Patients will complete the Voice Handicap Index-10 at this time. If patients are willing, they will also be enrolled on protocol 16C0061 for banking of biospecimens. During EUA, samples for research will be obtained from those patients who enroll on protocol 16C0061 for banking of biospecimens. Leukapheresis will be performed prior to the first dose of avelumab (see Section **4.1.1**).

Avelumab will be administered at a flat dose of 10 mg/kg IV every 2 weeks (+/- 3 days). EUA and endoscopy will be performed to assess airway, RRP lesion inflammation and to obtain research biopsies 2 weeks after the first dose of avelumab (9-17 days after the first dose). Leukapheresis will also be obtained at this time point. These procedures should occur before the second dose of avelumab. Disease response will first be assessed six weeks after the first dose of avelumab (+/- 7 days), which corresponds to the end of the first course (3 doses) of avelumab, by clinic-based endoscopic examination, Voice Handicap Index-10 and imaging if appropriate. These procedures should occur before the Course 2 Cycle 1 Day 1 dose of avelumab, if

applicable. If patients have a complete response or no response, treatment will be discontinued at that time. If patients have a partial response, treatment will be continued for up to 6 additional weeks (12 weeks total treatment) or until disease progression or complete response. If subjects demonstrate a partial response and receive an additional 6 weeks of treatment their responses will again be measured after completing this additional treatment (+/- 7 days). At the conclusion of treatment all patients will undergo EUA and endoscopy with either standard of care surgical debulking of their disease or biopsies to confirm complete regression of papillomatous disease. The primary endpoint of this study is complete response to treatment, but patients will be followed long-term after completion of treatment to assess timing and frequency of future interventions.

If a patient's condition precludes safe performance of any protocol-driven biopsy, apheresis or other research procedure, the procedure may be delayed for an additional two weeks or canceled at the discretion of the investigator. This will not be considered a protocol deviation. Endoscopy may be omitted in patients with disease that is not endoscopically accessible.

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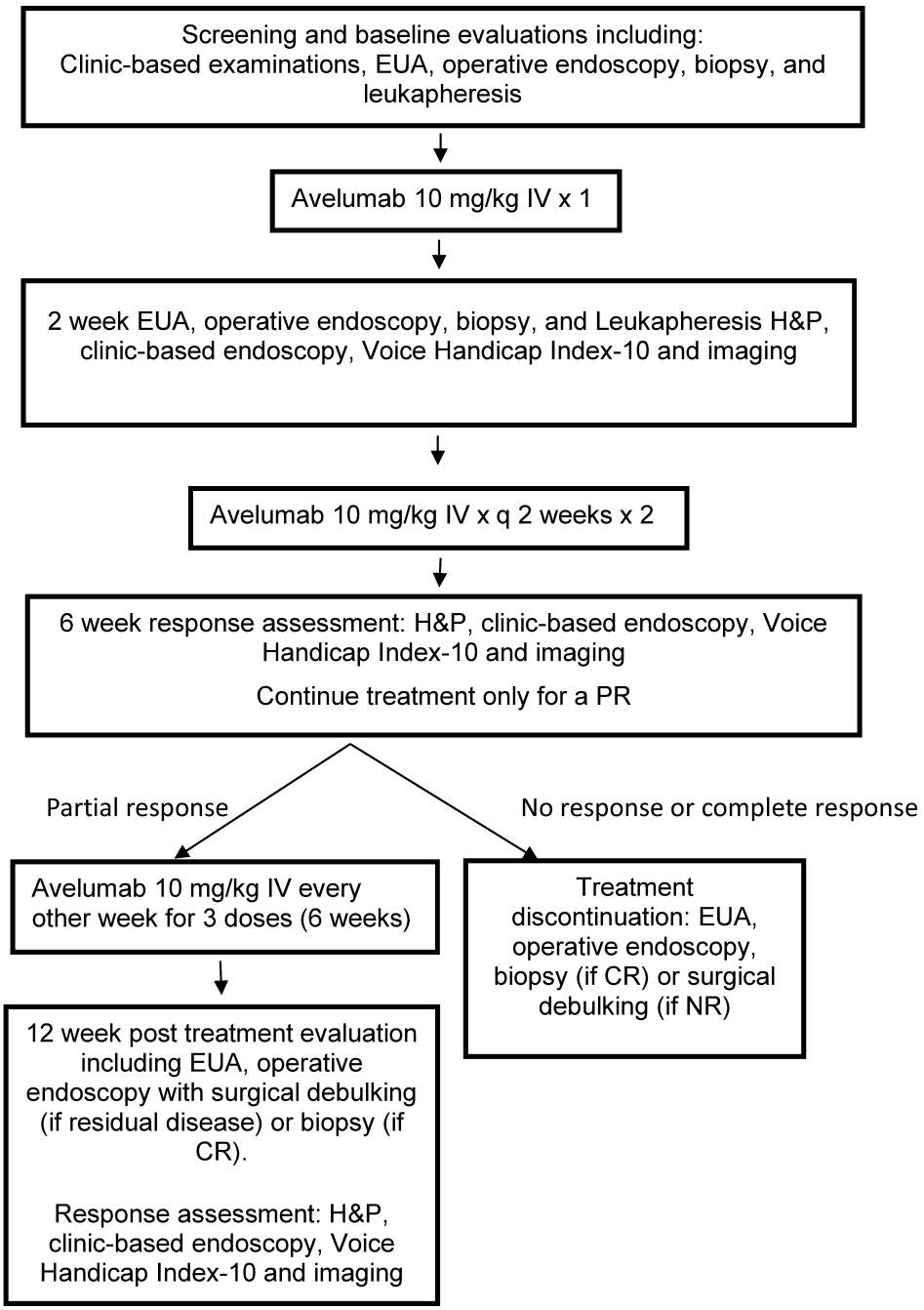
3.1.2 Protocol Schema



3.2 DRUG ADMINISTRATION

3.2.1 Avelumab

Avelumab will be administered at a dose of 10 mg/kg IV every other week for up to 12 weeks total (6 cycles). All patients will be pre-treated with an antihistamine and acetaminophen 30-60 minutes prior to each dose (for example, 25-50 mg diphenhydramine and 500-650 mg acetaminophen). Avelumab is to be diluted in 250 mL of 0.45% or 0.9% saline solution (sodium chloride injection) and administered as an IV infusion, using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified dose. It is not to be administered as an IV push or bolus injection.

Avelumab will be infused at 60 mL/hour for 10 minutes; if no infusion reaction observed then rate will be increased to 120 mL/hour for 10 minutes; if no infusion reaction observed then rate will be increased to 250 mL/hour for the remainder of the infusion. If infusion reactions are observed, the infusion rate may be decreased to the previous rate at which it was tolerated. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Avelumab will be infused in the NIH Clinical Center Day Hospital or on an inpatient oncology ward. Vital signs (blood pressure, pulse, respiration, temperature) will be assessed before infusion, at each rate change, at completion of infusion, and every 1 hour (+/- 15 minutes) or more frequently as clinically indicated for 2 hours after completion of the infusion or until stable.

Medications readily available for the emergency management of anaphylactoid reactions should include: epinephrine (1:1000, 1 mg/mL) for subcutaneous injection, diphenhydramine hydrochloride for intravenous injection, and resuscitation equipment.

3.2.1.1 Overall summary of the treatment plan

Drug	Dose	Days
Avelumab	10 mg/kg IV	Day 1 of a 14 day cycle (every other week) for up to 12 weeks total treatment (6 cycles)

Response will be assessed by flexible endoscopy with or without imaging studies before treatment and 6 and 12 weeks after starting treatment.

3.3 ON-STUDY ASSESSMENTS

If doses are delayed, assessments and research studies will be postponed accordingly.

3.3.1 Prior to each dose within 3 days of drug administration

- Targeted physical examination if clinically indicated which may include clinic-based flexible nasopharyngolaryngoscopy and/or tracheoscopy with assignment of a Derkay score if the Derkay score is being used as the primary response assessment
- Vital signs and oxygen saturation at rest and after exertion
- Assess for symptoms of myocarditis (chest pain, shortness of breath, swelling of ankles or feet)
- Pregnancy test in women of childbearing potential

- CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3
- TBNK
- Adverse events assessment
- Research blood:
  - 6 Cell Preparation Tubes (CPT) (48 mL) will be collected for immunological testing and processed as described in section **4.1.1**. Attention Jeremy Rose, Bldg. 10, room 12C216 contact phone: 301-594- 5339.
  - 1 Serum Separator Tubes (SST) (8 mL) will be obtained for serum collection and processed as described in section **4.1.1** . Attention Jeremy Rose, Bldg. 10, room 12C216 contact phone: 301-594-5339.
- Review of concomitant medications
- Voice Handicap Index-10 assessment questionnaire

3.3.2 Additional studies at a single time point two weeks after the first dose of avelumab

- Leukapheresis (see Section **4.1.1**)
- Exam under anesthesia (sedation or general anesthesia) including rigid and/or flexible endoscopy with biopsies to assess disease response, clinical signs of inflammation or airway compromise, and to obtain biopsies for research.

3.3.3 Every 6 week (3 cycles) (+/- 7 days) response assessment (performed at 6 and 12 weeks after first dose of avelumab)

- Interval targeted history and physical.
- Clinic-based flexible nasopharyngolaryngoscopy and/or tracheoscopy. This will include standard bright light endoscopy and videostroboscopy, and assignment of a Derkay score. This endoscopic examination combined with radiographic examination (if radiographically measurable disease is present) will be used to determine response to treatment.
- Voice Handicap Index-10 assessment questionnaire, see Section **12.2.**
- Imaging studies if imaging is used for response assessment.

3.3.4 Every 1 week between on-site assessments

- Telephone communication with patient to assess for any symptoms suggestive of an adverse event; this will be performed by physician or research nurse. Symptoms of myocarditis (chest pain, shortness of breath, swelling of ankles or feet) will be assessed.
- Laboratory studies as follows: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase and lipase.

3.3.5 At completion of treatment

- Targeted physical examination if clinically indicated which may include clinic-based flexible nasopharyngolaryngoscopy and/or tracheoscopy
- Vital signs and oxygen saturation at rest and after exertion
- Symptoms of myocarditis (chest pain, shortness of breath, swelling of ankles or feet) will be assessed
- Pregnancy test in women of childbearing potential
- CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3
- TBNK
- Adverse events assessment
- Research blood:
  - 6 CPT tubes (48 mL) will be collected for immunological testing and processed as described in section **4.1.1**. Attention Jeremy Rose, Bldg. 10, room 12C216 contact phone: 301-594- 5339.
  - 1 SST tube (8 mL) will be obtained for serum collection and processed as described in section **4.1.1** . Attention Jeremy Rose, Bldg. 10, room 12C216 contact phone: 301-594-5339.
- Clinic-based flexible nasopharyngolaryngoscopy and/or tracheoscopy. This will include standard bright light endoscopy and may include videostroboscopy, and assignment of a Derkay score if the Derkay score is being used for response assessment. This endoscopic examination will be used to assess treatment response.
- Imaging studies if imaging is used for response assessment.
- Voice Handicap Index-10 assessment questionnaire.
- Exam under anesthesia (sedation or general anesthesia) including rigid and/or flexible endoscopy with biopsies to perform standard of care papilloma debulking, to obtain biopsies for research and to validate complete response or the presence of persistent disease. These tests will be done 2 and 6 weeks after the first dose of avelumab for all patients. The same tests will be repeated 12 weeks after the first dose for patients that demonstrate a partial response and receive an additional 6 weeks of treatment.

3.3.6 Follow-up studies

- Patients who experience a complete response or partial response will be evaluated every 6 weeks x 3, then every 12 weeks x 3, then every 26 weeks x 2 or until disease progression (+/- 10 days for each time point). After completing the first 2 years' worth of follow up clinic visits, patients will be contacted annually (+/- one month)

for 3 years (a total of 5 years follow up) for patient status, dates of disease recurrence and interventions to treat recurrent disease.

- Patients who do not experience a response to treatment will be contacted annually (+/- one month) for 2 years following the last dose of study drug to document additional disease recurrence and treatments that they have received.
- Evaluations will include:
  - Interval directed history and physical
  - CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3
  - TBNK
  - Vital signs and oxygen saturation at rest and after exertion
  - Clinic-based flexible nasopharyngolaryngoscopy and/or tracheoscopy including standard bright light endoscopy and videostroboscopy with assignment of a Derkay score
  - Voice Handicap Index-10 assessment questionnaire.
  - Research blood: At each clinic visit and at subsequent time points at the discretion of the patient and the investigators:
    - 6 CPT tubes (48 mL) will be collected for immunological testing and processed as described in section **4.1.1**. Attention Jeremy Rose, Bldg. 10, room 12C216 contact phone: 301-594- 5339.
    - 1 SST tube (8 mL) will be obtained for serum collection and processed as described in section **4.1.1** . Attention Jeremy Rose, Bldg. 10, room 12C216 contact phone: 301-594-5339.
  - Adverse events will be followed until return to baseline or stabilization of event.
  - Imaging studies if imaging is used for response assessment.
  - Patients will be contacted 42 days (+/- 10 days) after the last dose of avelumab to check on patient's status.

3.4 DOSE MODIFICATIONS/DELAY

Dose modifications are not permitted.

3.4.1 Doses will be delayed for the following:

- Any Grade 2 or greater drug-related adverse event with the following exceptions:
  - Grade 2 skin rash or fatigue
  - Grade 2 infusion reaction in which the full dose of the drug is safely infused, per instructions in section **3.4.4**
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.
- Algorithms for management of toxicities are provided in Section **12.3.**

3.4.2 Resuming treatment

Subjects may resume treatment with avelumab under any of the following circumstances:

- Any grade 2 event that resolves to grade 1 or less within 14 days without systemic steroid treatment
- Grade 3/4 rash that improves to Grade 1/2 with treatment
- Grade 2/3/4 endocrinopathy that responds to treatment/replacement therapy

3.4.3 Discontinuing treatment

Treatment should be permanently discontinued for the following:

- Any Grade 3 or 4 drug-related adverse event with the exception of criteria listed in **3.4.2**

3.4.4 Avelumab infusion reactions

Since avelumab contains only human immunoglobulin protein sequences it is unlikely to be immunogenic and induce an infusion or hypersensitivity reaction. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the sponsor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4.0) guidelines.

NCI-CTCAE Grade	**Treatment Modification for Study Drug**
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Remain at bedside and monitor subject until recovery from symptoms. Decrease the study drug infusion rate by 50% and monitor closely for any worsening. Complete the remainder of the infusion at the reduced rate (50% of initial infusion rate). The total infusion time for study drug should not exceed 4 hours.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, corticosteroids, bronchodilators, IV fluids); prophylactic medications indicated for ≤ 24 hours.	Stop study drug infusion. Once infusion-related reaction has resolved or decreased to Grade 1 in severity, resume infusion at 25% of previous rate for 15 minutes, then increase to 50% of previous rate, and monitor closely for any worsening. The total infusion time for study drug should not exceed 4 hours.
Grade 3 or Grade 4 – severe or life-threatening; urgent intervention indicated. Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following	Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with

initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]). Grade 4: (life-threatening; pressor or ventilator support indicated).	methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids). Subjects must be withdrawn immediately from study drug treatment and must not receive any further study drug treatment.

IV = intravenous; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs.

Once the avelumab infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for all subsequent infusions. If a subject experiences a Grade 3 or 4 infusion-related reaction at any time, the subject must discontinue study drug.

3.4.5 Severe Hypersensitivity Reactions and Flu-Like Symptoms

If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. Subjects should be instructed to report any delayed reactions to the Investigator immediately.

For prophylaxis of flu-like symptoms, 25 mg of indomethacin or comparable nonsteroidal anti-inflammatory drug (NSAID) dose (for example, ibuprofen 600 mg, naproxen sodium 500 mg) may be administered 2 hours before and 8 hours after the start of each dose of avelumab IV infusion. Alternative treatments for fever (for example, paracetamol) may be given to subjects at the discretion of the Investigator.

3.4.6 Tumor Lysis Syndrome

In addition, since avelumab can induce antibody-dependent cell-mediated cytotoxicity, there is a potential risk of tumor lysis syndrome. Should this occur, subjects should be treated per the local guidelines.

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3.5 STUDY CALENDAR

Procedures	Screening	Baseline	Course 1				Course 2 (if indicated)				
			Cycle 1 Day 1	Cycle 2 Day 1	Cycle 3 Day 1	End of Course 1	Cycle 1 Day 1[o]	Cycle 2 Day 1	Cycle 3 Day 1	End of Treatment [a]	Follow-up [q,r]
History and PE[b]	X[f]	X[c,e]	X[c,e]	X[c]	X[c]	X[m]	X[c]	X[c]	X[c]	X	X
Vital signs, weight, O_2 saturation	X[f]	X[c,e]	X[c,e]	X[c]	X[c]		X[c]	X[c]	X[c]	X	X
Height		X									
ECOG Performance Score	X[f]										
Confirmation of diagnosis	X										
NIH Advance Directives Form[s]		X									
CBC with differential	X[c,e]	X[c,e]	X[c,e]	X[c]	X[c]	X[m]	X[c]	X[c]	X[c]	X	X
Chemistry panel including: LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, glucose, amylase, lipase, TSH, free T4, free T3[c]	X[c,e]	X[c,e]	X[c,e]	X[c]	X[c]	X[m]	X[c]	X[c]	X[c]	X	X
Antibody screen for Hepatitis B and C; HIV[p]	X[p]										

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Procedures	Screening	Baseline	Course 1				Course 2 (if indicated)				
			Cycle 1 Day 1	Cycle 2 Day 1	Cycle 3 Day 1	End of Course 1	Cycle 1 Day 1[o]	Cycle 2 Day 1	Cycle 3 Day 1	End of Treatment [a]	Follow-up [q,r]
Pregnancy test[c]	X[c,e]	X[c,e]	X[c,e]	X[c]	X[c]		X[c]	X[c]	X[c]	X	
TBNK[c]		X[c,e]	X[c,e]	X[c]	X[c]	X	X[c]	X[c]	X[c]	X	X
Imaging		X[e,f]				X[a,m,n]				X[m,n]	X[m,n]
ECG		X									
Clinic-based Flexible nasopharyngolaryngoscopy and/or tracheoscopy with Derkay score	X[f]		X[c,e]	X[i]	X[j]	X[k]	X[c]	X[c]	X[c]	X[m]	X
Voice Handicap Index-10			X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X	X
Exam under anesthesia with biopsies and possible debulking			X[h]	X[i]		X[k]				X[l]	
Research Blood[c]		X[c]	X[c]	X[c]	X[c]	X	X[c]	X[c]	X[c]	X	X
Adverse Events[c]				X[c]	X[c]	X	X[c]	X[c]	X[c]	X	X[d]
Concomitant Medications[c]		X[e]	X[c]	X[c]	X[c]	X	X[c]	X[c]	X[c]	X	
Leukapheresis			X[h]	X[i]							
Avelumab			X	X	X		X	X	X		

[a] End of Treatment studies will be performed 42 days (+/- 10 days) after the final Avelumab treatment.

[b] Complete H&P at baseline, directed H&P if clinically indicated before each dose (may include clinic-based flexible nasopharyngolaryngoscopy and/or tracheoscopy), directed H&P at response assessment.

[c] These procedures must be performed within 3 days before each dose of avelumab while on treatment.

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[d] Adverse events will be followed until return to baseline or stabilization of event.

[e] If the screening and baseline tests were performed prior to 3 days before the first dose of avelumab they will need to be repeated before the start of treatment. Refer to section **2.2** for screening evaluation timing requirements.

[f] Within 14 days prior to subject enrollment

[g] Within 28 days prior to subject enrollment

[h] Within 7 days prior to first dose of avelumab

[i] 9-17 days after first dose of avelumab and before second dose of avelumab

[j] 9-17 days after second dose of avelumab and before third dose of avelumab

[k] 9-17 days after third dose of avelumab and before the Course 2 Cycle 1 Day 1 dose, if applicable

[l] 9-17 days after last dose of avelumab

[m] +/- 10 days

[n] If imaging is used for response assessment

[o] Tests performed for End of Course 1 time point that were completed within 7 days prior to the Course 2 Cycle 1 Day1 dose of avelumab do not need to be repeated for Course 2 Cycle 1 Day 1.

[p] within 90 days prior to subject enrollment

[q] Patients who experience a complete response or partial response will be evaluated every 6 weeks x 3, then every 12 weeks x 3, then every 26 weeks x 2 (+/- 10 days for each time point during the first two years) or until disease progression. After completing the first 2 years' worth of follow up clinic visits, patients will be contacted annually (+/- one month) for 3 years (a total of 5 years follow up) via phone or email for patient status, dates of disease recurrence and interventions to treat recurrent disease. The first follow-up visit, which occurs 42 days (+/- 10 days) after last study treatment, will satisfy safety visit requirements as noted in section **3.6**. If unwilling or unable to travel to the NIH Clinical Center for follow-up visits, patients will be contacted by telephone regarding their status, and may be asked to send labs and physical exam reports to fulfill visit requirements.

[r] Patients who do not experience a response to treatment will be contacted annually (+/- one month) for 2 years following the last dose of the study drug to document additional disease recurrence and treatments that they have received. For the safety follow-up visit which should occur approximately 42 days (+/- 10 days) after last study treatment (as noted in section **3.6**), if unwilling or unable to travel to the NIH Clinical Center, patients will be contacted by telephone regarding their status, and may be asked to send labs and physical exam reports to fulfill end of treatment safety follow-up visit requirements. Annual follow-up contact may occur via telephone.

[s] As indicated in section **9.3,** all subjects will be offered the opportunity to complete an NIH advance directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required.

3.6 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to documenting removal from study, effort must be made to have all subjects complete a safety visit approximately 42 days (+/- 10 days) following the last dose of study therapy.

3.6.1 Criteria for removal from protocol therapy

Patients will be taken off treatment for the following:

- Completion of protocol therapy
- Participant requests to be withdrawn from active therapy
- The patient receives any other treatment for RRP or requires the use of any corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications.
- General or specific changes in the patient's condition render the patient unacceptable for further treatment on this study in the judgment of the investigator.
- Any Grade 3/4 drug-related adverse events with the exceptions as detailed in section **3.4**.
- Disease progression
- Participant becomes pregnant

3.6.2 Duration of Follow up

Patients who do not experience a complete response will be contacted annually for two years after the 42 day (+/- 10 days) follow up visit to determine the date of disease recurrence following completion debulking on this study and the dates and types of additional interventional procedures to control RRP. Patients who experience a complete response will be contacted annually for three years after completing the first 2 years' worth of follow up clinic visits (for a total of approximately five years of follow up). The dates of disease recurrence and interventions to treat recurrent disease will be recorded.

3.6.3 Off-Study Criteria

Patients will be taken off study for the following:

- The patient voluntarily withdraws
- There is significant patient noncompliance
- The investigators decide it is in the patient's best interest
- The patient completes follow-up
- Death

3.7 STOPPING RULE

3.7.1 All protocol treatment will be temporarily stopped to allow for review of data and consultation with the FDA and IRB if either of the following events occur:

- Any treatment-related death
- Three ≥ Grade 3 Unexpected Serious Adverse Events

3.7.2 All protocol treatment will be temporarily stopped to allow review of interim summary of safety and efficacy following completion of the pilot cohort prior to expanding enrollment.

4 BIOSPECIMEN COLLECTION

Biospecimen collection on this protocol will consist of blood draws, leukapheresis products, and biopsies of papillomas and adjacent tissue.

4.1 CORRELATIVE STUDIES FOR RESEARCH

4.1.1 Biospecimen collection before the start of avelumab

- Patients will also be invited to enroll on protocol 16C0061 for which patients must consent separately.
- Blood will be collected for research purposes. A total of 12 CPT tubes (8 mL each of blood) will be collected prior to the first dose of avelumab. This is a total of 96 mL of blood. This blood will be used for immunology assays. This blood can be collected on different days as long as a total of 12 CPT tubes are collected prior to the first dose of avelumab. One CPT tube will be used to collect plasma which will be frozen in a 4mL vial. PBML from the remainder of the CPT tubes will be frozen in aliquots of 10 x 10^6 cells/vial. Send to ETIB's Pre-Clinical Core lab; Attention Jeremy Rose, Bldg. 10, room 12C216 contact phone: 301-594-5339.
- 16 mL of blood will be drawn to obtain serum for research purposes (2 SST tubes, 8 mL per tube) within 14 days prior to the first dose of avelumab. This will be processed in ETIB Pre-Clinical Core and frozen in aliquots of 0.5-1mL/vial. Send to ETIB's Pre-Clinical Core lab; Attention Jeremy Rose, Bldg. 10, room 12C216 contact phone: 301-594-5339.
- A research apheresis sample will be collected prior to first dose of avelumab. Apheresis collection will be 5 L volume (as close to 5 L as possible). Apheresis will only be performed on patients with adequate peripheral venous access. Cells will be transferred to ETIB 's Pre-Clinical Core lab, Attention Jeremy Rose, Bldg. 10, room 12C216, contact phone: 301-594-5339. Aliquots of PBMC and plasma will be cryopreserved for immunological monitoring. Cell product will be frozen in 10 vials at concentration 100 x106 cells/mL and additional vials at 300 x 106 cells/mL.Papilloma and adjacent tissue samples will be collected by biopsy prior to the first dose of avelumab. Biopsies will be obtained with rigid or flexible endoscopy under sedation or general anesthesia. They will consist of up to 10 papilloma fragments, each 1-3 mm in diameter. One fragment may be sent to pathology for permanent sections. The other fragments of the biopsy will be sent to Dr. Hinrichs' laboratory in sterile 1.5 mL Eppendorf tubes with a small amount of sterile normal saline. Additional tissue that is removed to debulk papillomas may also be collected for research. Up to two fragments of normal mucosa, each 1-3 mm in diameter, will also be obtained and sent to Dr. Hinrichs' laboratory. Send to Dr. Hinrichs' lab; Building 10, Room 4B04.

- Patients with papillomas that cannot be biopsied by endoscopy may participate in the trial. All tissue specimen collection except papilloma biopsies will be performed.
- Specimens will be cataloged and stored in ETIB's Pre-Clinical Core lab. Assays will be performed retrospectively.

4.1.2 Biospecimen collection during treatment and follow-up

- Patients will return to the Clinical Center every two weeks for avelumab dosing. Blood and serum for research and TBNK testing will be obtained prior to each dose of avelumab. Blood for research will consist of:
  - 6 CPT tubes of Research Blood (48 mL) will be collected for immunological testing and processed as described in section **4.1.1**. Attention Jeremy Rose, Bldg. 10, room 12C216 contact phone: 301-594- 5339.
  - 1 SST tube (8 mL) of Research Blood will be obtained for serum collection and processed as described in section **4.1.1** . Attention Jeremy Rose, Bldg. 10, room 12C216 contact phone: 301-594-5339.
- Papilloma and adjacent tissue samples will be collected by biopsy 2 weeks after the first dose of avelumab (9-17 days after the first dose). This should occur prior to second dose of avelumab. Repeat biopsies will be collected again two weeks after the third dose of avelumab (9-17 days after the third dose), which corresponds to the end of the first course (3 doses) of avelumab. These procedures should occur before Course 2, if applicable. Biopsies will again be collected at the time of completion debulking for patients who do not experience a complete tumor response. Biopsies will be obtained with rigid or flexible endoscopy under sedation or general anesthesia. They will consist of up to 10 papilloma fragments, each 1-3 mm in diameter. One fragment may be sent to pathology for permanent sections. The other fragments of the biopsy will be sent to Dr. Hinrichs' laboratory in sterile 1.5 mL Eppendorf tubes with a small amount of sterile normal saline. Up to two fragments of normal mucosa, each 1-3 mm in diameter, will also be obtained and sent to Dr. Hinrichs' laboratory. Send to Dr. Hinrichs' lab; Building 10, Room 4B04; Attention: Stacey Doran, MD 301-451-6957.
- A research apheresis sample will be collected 2 weeks after the first dose of avelumab (9-17 days after the first dose). This apheresis should occur before the second dose of avelumab. Apheresis will only be performed on patients with adequate peripheral venous access. Cells will be transferred to ETIB 's Pre-Clinical Core lab, Attention Jeremy Rose, Bldg. 10, room 12C216, contact phone: 301-594-5339. Aliquots of PBMC and plasma will be cryopreserved for immunological monitoring. Cell product will be frozen in 10 vials at concentration 100 x106 cells/mL and additional vials at 300 x 106 cells/mL.If patients experience a complete response, they will continue to be followed every 6 weeks x 3, then every 12 weeks x 3, then every 26 weeks x 2. Research blood and TBNK will be collected at these time points as described above.

4.1.3 Research studies

- Biospecimens will be collected for research to identify biomarkers of response, understand the mechanism of action of the treatment, and investigate the biology of RRP.

- Research studies will be considered exploratory analyses and will include all or some of the following: assessment of PD-L1 expression by papillomas and papilloma-infiltrating immune cells, testing of papillomas and normal appearing mucosa for HPV, and evaluation of papilloma-infiltrating T cell responses against HPV antigens.
  - Testing of papilloma-infiltrating T cells and peripheral blood T cells for recognition of HPV antigens [25].

    Generation and isolation of T cells

    Papilloma-infiltrating T cells will be generated from papilloma biopsy specimens by culture of 2 mm tissue fragments in culture media with IL-2. Lymphocyte cultures will be split when confluent and cryopreserved when sufficient cells have been generated. Flow cytometry may be performed to assess the lymphocyte populations using markers such as CD3, CD4, CD8, and CD56 to assess lymphocyte subtypes. T cells will be isolated from peripheral blood samples by magnetic bead separation using standard techniques from commercially available kits (Miltenyi or similar).

    HPV-specific T cell response assays

    Target cells for assays measuring HPV-specific T cells responses will be autologous immature dendritic cells (DCs) generated from apheresis samples. The DCs will be loaded with pools of overlapping peptides spanning each of the viral antigens encoded by HPV. Reactivity against each antigen will be assessed separately. Immunological assays may consist of interferon-gamma ELISPOT, interferon-gamma production as determined by ELISA, 4-1BB upregulation, and or intracellular cytokine production as described previously [25].

    HPV detection and genotyping

    Testing will be performed by Dr. Hinrichs' laboratory using PCR-based type-specific HPV detection and quantification assays [25].

    Generation of papilloma cell lines.

    When feasible, papilloma biopsy specimens will be sent to Richard Schlegel's laboratory for the generation of papilloma cell lines for use in research at Georgetown University Medical Center. The specimens will be provided in a tube of sterile saline or similar sterile buffer. The specimens will be deidentified. The source of the specimens will be known to the NIH investigators but not the Georgetown University investigators.

    Richard Schlegel M.D., Ph.D.
    Professor and Oscar B. Hunter Chair
    Chair, Department of Pathology
    Director, Center for Cell Reprogramming
    Research Building, Room W500
    Georgetown University Medical School
    3900 Reservoir Road, NW
    Washington, DC 20057
    Telephone: 202-687-1655

Transportation to Dr. Schlegel's laboratory will be provided by courier. The courier will be Washington Express. The contact information for Washington Express is:

www.washingtonexpress.com

800-939-5463

4.1.4 Co-Enrollment on 16C0061 / Biobanking

Samples from patients may be transferred to protocol 16C0061 for biobanking of specimens if the patient has consented to that study.

4.1.5 Sample Storage, Tracking and Disposition

Preclinical Development and Clinical Monitoring Facility

- Samples will be archived by the ETIB Preclinical Development and Clinical Monitoring Facility (PDCMF). All data associated with archived clinical research samples is entered into the ETIB PDCMF's Microsoft Excel databases on frozen cells and plasma. These databases are stored on the NCI group drive in the ETIB 'PRECLINSERVICE' folder. Access to this folder is limited to PDCMF staff and ETIB clinical staff, requiring individual login and password. All staff in the PDCMF laboratory receives annually updated NIH/CIT training and maintains standards of computer security.
- The data recorded for each sample includes the patient ID, trial name/protocol number, date drawn, treatment cycle/post-transplant time point, cell source (e.g. peripheral blood, lymph apheresis, mobilized peripheral blood stem cells, marrow, urine, skin or oral biopsy) as well as box and freezer location. Patient demographics that correlate treatment outcomes and therapies with the samples can be obtained only through the NCI/ETIB clinical records. As of January 2007, all newly received samples receive a unique bar code number, which is included in the sample record in the PDCMF database. Only this bar code is recorded on the sample vial and the vials will not be traceable back to patients without authorized access to the PDCMF database. All non-coded samples previously archived will be stripped of identifiers prior to distribution for any use other than as a primary objective of the protocol under which they were collected.
- Samples are stored in locked freezers. All samples will be labeled solely with a bar code (which includes the date, and serially determined individual sample identifier). The key will be available to a restricted number of ETIB investigators and associate investigators on the protocol. Coded samples will be stored frozen at -20°, -80° or liquid nitrogen vapor phase according to the stability requirements under the restricted control of the PDCM Facility of ETIB.
- Access to samples from a protocol for research purposes will be by permission of the Principal Investigator of that protocol in order to be used (1) for research purposes associated with protocol objectives for which the samples were collected, or (2) for a new research activity following submission and IRB approval of a new protocol and consent, or (3) for use only as unlinked or coded samples under the OHSRP Exemption Form guidelines stipulating that the activity is exempt from IRB review. Unused samples must be returned to the PDCMF laboratory.

- Samples, and associated data, will be stored permanently unless the patient withdraws consent. If researchers have samples remaining once they have completed all studies associated with the protocol, they must be returned to the PDCMF laboratory.
- These freezers are located onsite at the PDCMF laboratory (12C216) or in ETIB common equipment space (CRC/3-3273).

4.1.5.1 Hinrichs laboratory

- Samples may be transferred from Preclinical Development and Clinical Monitoring Facility to the Hinrichs laboratory for the research studies indicated in **4.1.3**.
- Samples transferred to the Hinrichs laboratory will be barcoded and tracked with LabMatrix.
- Laboratory research data will be stored on the NCI secure server in the Hinrichs laboratory folder with secure access by laboratory personnel only.

4.1.6 Protocol Completion/Sample Destruction

- Once research objectives for the protocol are achieved, researchers can request access to remaining samples, providing they have both approval of the Principal Investigator of the original protocol under which the samples or data were collected and either an IRB approved protocol and patient consent or the OHSRP Exemption Form stipulating that the activity is exempt from IRB review.
- The PDCMF staff will report to the Principal Investigators any destroyed samples, if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container), lost in transit between facilities or misplaced by a researcher.

  The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **6.2**.

5 DATA COLLECTION AND EVALUATION

5.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Patients will be followed for adverse events for minimum of 30 days after removal from study treatment or until off-study, whichever comes first.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

End of study procedures: Data will be stored according to HHS, FDA regulations and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **6.2.1**.

5.1.1 Concomitant medications recording:

Only medications used to treat adverse events related to the study medication will be recorded in the data base.

5.1.2 Collection of recurrence and subsequent treatments

The dates of disease recurrences following completion of treatment and/or debulking on this study and the dates and types of additional interventional procedures to control RRP will be recorded.

5.1.3 Collection of Adverse Events following surgery/procedure

Grade 1 or 2 adverse events that are clearly attributable to surgery/procedure will not be recorded.

5.1.4 Collection of Adverse Events during Follow-up

Adverse Events that occur during the follow-up period will only be recorded if they are considered related to the avelumab.

5.2 RESPONSE CRITERIA

Disease stage and response will be determined by flexible nasopharyngolaryngoscopy and/or tracheoscopy using the Derkay staging system if the patient does not have pulmonary disease and/or by imaging if the patient has pulmonary disease [6]. The Derkay staging system has been validated with a high degree of inter-rater reliability [16]. It incorporates an objective score based on the number of sites and bulkiness of papillomas within the pharynx, larynx and trachea and a subjective score determined by voice and breathing symptoms. Physical exam and/or clinic-based endoscopy will be used to visualize all accessible papillomas and assign an objective score using the Derkay system. Only lesions that can be visualized by clinic-based flexible nasopharyngolaryngoscopy and/or tracheoscopy will be included in the baseline score used for assessing treatment response. This score must be 10 or greater for patients to be eligible

for treatment. If patients have disease that is better visualized or only visualized with an imaging study such as CT scan or MRI then imaging studies will be obtained. Preliminary Derkay scores and response assessment will be determined by the endoscopist performing the procedure. Final reporting of clinical responses will be based on a blinded review of endoscopic video and or photos by one or more independent otolaryngologists.

Response and progression from imaging studies will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [26]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

If a subject has disease being assessed by imaging for response and refuses clinic-based flexible nasopharyngolaryngoscopy and/or tracheoscopy, no Derkay score will be calculated. This will not be considered a protocol deviation.

5.2.1 Baseline assessment

- All accessible disease will be examined by physical exam and/or endoscopy to establish a baseline.
- Only lesions visualized by clinic-based flexible nasopharyngolaryngoscopy and/or tracheoscopy will be included in the baseline objective Derkay score.
- Imaging studies will be performed if appropriate and baseline measurements determined using RECIST 1.1 criteria.

5.2.2 Definition of measurable disease

- Any papilloma that can be visualized via clinic-based endoscopy and assigned a score using the Derkay system
- Any papilloma that can be measured by imaging using RECIST 1.1 criteria.

5.2.3 Definition of disease response

5.2.3.1 Complete Remission (CR)

All criteria must be met.

- No evidence of papillomas on physical exam and/or clinic-based flexible nasopharyngolaryngoscopy and/or tracheoscopy.
- No evidence of papillomas by exam under anesthesia (sedation or general anesthesia) with endoscopy and biopsies.
- Absence of disease by imaging if lesions are assessed by imaging.

5.2.3.2 Partial response (PR)

Either criterion may be met.

- Decrease in Derkay anatomic score of 30 percent or greater
- Partial tumor response by imaging using RECIST 1.1 criteria

5.2.3.3 Progressive disease (PD)

Any criterion may be met.

- Increase in objective Derkay anatomic score of 50 percent or greater
- Disease progression by imaging using RECIST 1.1 criteria
- New or worsening symptoms attributable to growth of papillomas or new papillomas.

5.2.3.4 Stable disease

- Not meeting criteria for CR, PR, or PD.

5.2.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.

***	In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note:	Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

5.3 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

6 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

6.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found here.

6.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

6.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here. Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

6.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here.

6.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reported to the OHSRP in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at NCICCRQA@mail.nih.gov within one business day of learning of the death.

6.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

6.4.1 Principal Investigator/Research Team

The clinical research team will meet every two weeks when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator. Events meeting requirements for expedited reporting as described in section **6.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7 SPONSOR PROTOCOL/SAFETY REPORTING

7.1 DEFINITIONS

7.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2))

7.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see section **7.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
    - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient or subject convenience) is not considered a serious adverse event.
    - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon

appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32)

7.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 4.0.

7.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.

- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

7.1.6 Adverse Events of Special Interest (AESI)

Myocarditis or other serious autoimmune AEs (even if such events are expected) that occur will be reported by the PI and/or study coordinator. These AEs will be submitted to the FDA Division of Antiviral Products (DAVP) by the sponsor.

7.2 Assessment of Safety Events

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.

- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to section **6.1**. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor.

7.3 Reporting of Serious Adverse Events

Any AE that meets protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form.

All SAE reporting must include the elements described in section **7.2**.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=157942842

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

7.4 Safety Reporting Criteria to the Pharmaceutical Collaborators

Reporting will be per the collaborative agreement.

The CCR Office of Regulatory Affairs will send all reports to the manufacturer as described below.

7.4.1 Serious and Unexpected Suspected Adverse Reaction (SUSAR)

Definition: A suspected adverse reaction to study treatment that is both serious and unexpected. SUSARs will be reported within 24 hours of learning of the event to EMD Serono's parent company, Merck via Fax: 781-681-2961 or email: ICSR_CT_GPS@merckgroup.com.

7.4.2 Serious Adverse Event (SAE)

Definition: See Section **6.1.5**. SAEs will be reported within 24 hours of learning of the event to EMD Serono's parent company, Merck via Fax: 781-681-2961 or email: ICSR_CT_GPS@merckgroup.com.

7.4.3 Pregnancy

The Investigator must report any pregnancy occurring in a subject treated with the study drug during the course of the study. The Investigator shall ensure that the case is followed up to the end of the pregnancy and provide all relevant documentation and a final report on the outcome to Merck.

7.4.4 Annual Report

7.5 THE SPONSOR WILL PROVIDE A COPY OF THE FDA ANNUAL REPORT TO EMD SERONO/MERCK AT THE TIME OF SUBMISSION TO THE FDA.REPORTING PREGNANCY

7.5.1 Maternal exposure

If a participant becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy becomes known.

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (section **7.1.2**) should be reported as SAEs.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented.

7.5.2 Paternal exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 60 days after the last dose of avelumab.

Pregnancy of the participant's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 60 days after the last dose should, if possible, be followed up and documented.

7.6 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

8 CLINICAL MONITORING

As a sponsor for clinical trials, FDA regulations require the CCR to maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary and secondary study endpoints; adherence to the protocol, regulations, ICH E6, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation

- Drug administration and accountability
- Adverse events monitoring
- Response assessment.

The monitoring program also extends to multi-site research when the CCR is the coordinating center.

This trial will be monitored by personnel employed by a CCR contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

9 STATISTICAL CONSIDERATIONS

The trial will be conducted using a Simon optimal two-stage design; the objective is to rule out a 5% complete response rate (p0=0.05) and target a 20% complete response rate (p1=0.20).

The design will use alpha=0.10 (10% chance of accepting a poor agent) and beta=.10 (corresponding to 90% power--and 10% chance of incorrectly rejecting a promising agent). The first stage of accrual will consist of 12 evaluable patients. If 0/12 has a complete clinical response, then no further patients would be enrolled to that cohort. Should 1 or more patients in the first 12 have a complete response, then accrual would continue until a total of 37 evaluable patients have enrolled. If there are 1 to 3 complete responses in 37 patients, this would be considered unacceptably low, while if 4 or more patients have complete responses in 37 patients, then the results will be considered sufficiently promising for further evaluation. Under the null hypothesis (5% complete response rate), the probability of early termination is 54.0%.

It is anticipated that up to 2 patients per month may enroll onto this trial; thus, up to 2 years may be required to complete accrual. The trial would require up to 37 total evaluable patients; the accrual ceiling will be set at 40 patients to allow for a small number of inevaluable patients.

10 COLLABORATIVE AGREEMENT

10.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT

- The study drug avelumab will be provided under a CRADA (EMD Serono, Inc – NCI CRADA# 02666/NCI MTA # 41332-16) between the manufacturer, EMD Serono, and the Center for Cancer Research, National Cancer Institute.

10.2 MATERIAL TRANSFER AGREEMENT

- An MTA is in place with Georgetown University Medical School (NCI MTA# 42132-17) for the samples discussed in section **4.1.3**

11 HUMAN SUBJECTS PROTECTIONS

11.1 RATIONALE FOR SUBJECT SELECTION

The patients to be entered in this protocol have RRP involving multiple anatomic sites and requiring repeated procedures for disease control. There is no curative therapy for these patients and their disease causes substantial morbidity and occasional mortality. Subjects from both genders and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. To date, there is no information that suggests that differences in disease response would be

expected in one group compared to another. Efforts will be made to extend accrual to a representative population, but in this preliminary study, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic and/or ineffective treatments on the one hand and the need to explore gender and ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to gender or to ethnic identity are noted, accrual may be expanded or a follow-up study may be written to investigate those differences more fully.

There is no effective systemic therapy for patients with RRP.

RRP causes death by airway compromise, mass effect in the lungs, and transformation into invasive cancer.

11.2 Participation of Children

Because no dosing or adverse event data are currently available on the use of avelumab in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

11.3 Participation of Pregnant Women

Based on its mechanism of action and data from animal studies, avelumab can cause fetal harm when administered to a pregnant woman. Human IgG1 is known to cross the placental barrier and avelumab is an immunoglobulin G1 (IgG1); therefore, avelumab has the potential to be transmitted from the mother to the developing fetus. Given these risks, pregnant women will be excluded from this study and patients of both genders must be willing to practice contraception for at least 28 days prior, throughout the avelumab treatment and for at least 60 days after avelumab treatment.

11.4 Evaluation of Benefits and Risks/Discomforts

The experimental treatment has a chance to provide clinical benefit though this is unknown. The safety profile of avelumab has been established in treatment of over 700 patients. The risks are well-characterized and the toxicities are generally reversible. RRP carries the risk of repeated procedures to control the disease and the potential for airway compromise, lung compression and infection, and transformation to invasive cancer. If this study has a positive outcome it will provide benefit to not only the patients on the study but also to future patients. This study may also contribute to our knowledge of the mechanism of action of avelumab and the biology or RRP that will help to advance treatment of RRP and other diseases.

11.4.1 Study drug risks

The risks associated with the study product are discussed in Section **10.1.4**.

11.4.2 EUA and Biopsy Risks

EUA is associated with the risk of sedation or general anesthesia. Complications of general anesthesia are rare. Serious risks include allergic reaction to a drug, loss of airway control and ventilation, and cardiovascular complications such as hypotension, dysrhythmia, or myocardial infarction, and neurological complications such as stroke or brain damage. The risks associated with biopsies are pain and bleeding at the biopsy site. Rarely, there is a risk of infection at the biopsy site. The anesthesia and biopsies of the initial evaluation have the benefit of confirming

the diagnosis and the extent of the disease, and permitting debulking of disease that poses a major airway risk. Similarly, the anesthesia and biopsies at the completion of treatment will either confirm a complete response or will be performed in association with papilloma debulking according to standard of care therapy.

11.4.3 Risks associated with blood sampling

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting.

11.4.4 Risks associated with leukapheresis

Risks may involve bleeding at the apheresis site and lightheadedness. Decrease in blood pressure is considered a less common risk.

11.4.5 Risks associated with CT scans

If patients have disease that is better visualized or only visualized with an imaging study such as CT scan or MRI, then imaging studies will be obtained. If a CT scan is used, there will also be a risk of exposure to radiation from up to 3 CT scans. The amount of radiation received in this study is 0.43 rem which is below the guideline of 5 rem (or 0.5 rem in children) per year allowed for research subjects by the NIH Radiation Safety Committee.

11.5 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided to the participant for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms) per discretion of the designated study investigator and with the agreement of the participant. Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

12 PHARMACEUTICAL INFORMATION

12.1 AVELUMAB IND# 130884

Amino Acid Sequence: 4 polypeptide chains, which include 2 identical heavy chains with 440 amino acids and 2 identical light chains.

Other Names: MSB0010718C

Classification: Anti-PD-L1MAb

M.W.: 143,832 daltons

12.1.1 Mode of Action

Avelumab targets the programmed death–ligand 1 (PD-L1). PD-1 is a negative regulatory receptor expressed by activated T and B lymphocytes. Binding of PD-1 to its ligand, PD-L1, results in the down-regulation of lymphocyte activation. Avelumab inhibits the binding of PD-1 to PD-L1. Inhibition of the interaction between PD-1 and PD-L1 promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens.

12.1.2 Description

Avelumab drug product is a sterile, clear, and colorless concentrate for solution intended for intravenous (i.v.) administration. The drug is presented at the concentrations of 10 mg/mL and 20 mg/mL in single-use glass vial containing 80 mg and 200 mg of avelumab, respectively.

12.1.3 Source

Avelumab is an investigational agent that will be supplied to the NIH Pharmacy by EMD Serono.

12.1.4 Toxicities

As of 01 June 2015, safety data of 717 subjects who were treated with 10 mg/kg of avelumab every 2 weeks and followed up for at least 4 weeks in the pooled tumor expansion cohort of Trial EMR 100070-001 were evaluated.

The most frequently observed treatment-related TEAEs (with an incidence of ≥ 2%) of any grade in the pooled expansion cohort were infusion-related reaction, fatigue , nausea, diarrhea, chills, and decreased appetite. Other frequently seen treatment-related TEAEs with an incidence < 5% but ≥ 2% included arthralgia, pyrexia, hypothyroidism, pruritus, vomiting, influenza-like illness, rash, anemia, AST increased, myalgia, asthenia, headache, ALT increased, dyspnea, and constipation.

Note: On this protocol, dry mouth has been observed with greater frequency than previously observed, from a CTCAE grade 1-2 intensity, and may be attributable to avelumab. This has been noted in the informed consent document.

12.1.5 Preparation

Avelumab drug product must be diluted in 250 mL of 0.45% or 0.9% saline solution (sodium chloride injection) supplied in an infusion bag. Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the manual of preparation.

Prior to the preparation of the dilution for final infusion, allow each vial to equilibrate to room temperature. Use a disposable syringe equipped with a needle of suitable size to remove a volume of sodium chloride solution to be replaced by avelumab from the infusion bag and discard the removed solution. Use a new disposable syringe equipped with a needle of suitable size to inject a volume of avelumab drug product identical to the discarded volume of sodium chloride solution into the infusion bag. Gently invert the mixture 10 times. Infusion bags must not be shaken, in order to avoid foaming or excessive shearing of the protein solution. The preparation must be carefully inspected as it should result in a homogeneous looking clear solution, free of visible particles.

12.1.6 Storage and Stability

Avelumab drug product must be stored at 2°C to 8°C until use, and it must not be frozen. Rough shaking of avelumab product must be avoided. Avelumab drug product must be diluted with 0.45% or 0.9% saline solution. It is recommended that the diluted avelumab solution is used immediately.

12.1.7 Administration procedures

Avelumab is to be administered as an IV infusion, using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified dose. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

12.1.8 Potential Drug Interactions

No formal drug interaction trials have been conducted with avelumab in humans.

13 REFERENCES

1. Mounts, P., K.V. Shah, and H. Kashima, *Viral etiology of juvenile- and adult-onset squamous papilloma of the larynx.* Proc Natl Acad Sci U S A, 1982. **79**(17): p. 5425-9.
2. Derkay, C.S., *Task force on recurrent respiratory papillomas. A preliminary report.* Arch Otolaryngol Head Neck Surg, 1995. **121**(12): p. 1386-91.
3. Silver, R.D., et al., *Diagnosis and management of pulmonary metastasis from recurrent respiratory papillomatosis.* Otolaryngol Head Neck Surg, 2003. **129**(6): p. 622-9.
4. Dedo, H.H. and K.C. Yu, *CO(2) laser treatment in 244 patients with respiratory papillomas.* Laryngoscope, 2001. **111**(9): p. 1639-44.
5. Derkay, C.S. and B. Wiatrak, *Recurrent respiratory papillomatosis: a review.* Laryngoscope, 2008. **118**(7): p. 1236-47.
6. Armstrong, L.R., C.S. Derkay, and W.C. Reeves, *Initial results from the national registry for juvenile-onset recurrent respiratory papillomatosis. RRP Task Force.* Arch Otolaryngol Head Neck Surg, 1999. **125**(7): p. 743-8.
7. Kashima, H.K., et al., *A comparison of risk factors in juvenile-onset and adult-onset recurrent respiratory papillomatosis.* Laryngoscope, 1992. **102**(1): p. 9-13.
8. *Nivolumab Investigator Brochure, BMS-936558, MDX1106.* 2013.
9. Woo, S.R., et al., *Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape.* Cancer Res, 2012. **72**(4): p. 917-27.
10. Taube, J.M., et al., *Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape.* Sci Transl Med, 2012. **4**(127): p. 127ra37.
11. Thompson, R.H., et al., *Costimulatory B7-H1 in renal cell carcinoma patients: Indicator of tumor aggressiveness and potential therapeutic target.* Proc Natl Acad Sci U S A, 2004. **101**(49): p. 17174-9.
12. Thompson, R.H., et al., *Costimulatory molecule B7-H1 in primary and metastatic clear cell renal cell carcinoma.* Cancer, 2005. **104**(10): p. 2084-91.
13. Thompson, R.H., et al., *Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up.* Cancer Res, 2006. **66**(7): p. 3381-5.
14. Ohigashi, Y., et al., *Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer.* Clin Cancer Res, 2005. **11**(8): p. 2947-53.
15. Wu, C., et al., *Immunohistochemical localization of programmed death-1 ligand-1 (PD-L1) in gastric carcinoma and its clinical significance.* Acta Histochem, 2006. **108**(1): p. 19-24.
16. Dong, H. and L. Chen, *B7-H1 pathway and its role in the evasion of tumor immunity.* J Mol Med (Berl), 2003. **81**(5): p. 281-7.

17. Nomi, T., et al., *Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer.* Clin Cancer Res, 2007. **13**(7): p. 2151-7.

18. Zitvogel, L., A. Tesniere, and G. Kroemer, *Cancer despite immunosurveillance: immunoselection and immunosubversion.* Nat Rev Immunol, 2006. **6**(10): p. 715-27.

19. Venkatesan, N.N., H.S. Pine, and M.P. Underbrink, *Recurrent respiratory papillomatosis.* Otolaryngol Clin North Am, 2012. **45**(3): p. 671-94, viii-ix.

20. Smith, E.M., et al., *Human papillomavirus infection in papillomas and nondiseased respiratory sites of patients with recurrent respiratory papillomatosis using the polymerase chain reaction.* Arch Otolaryngol Head Neck Surg, 1993. **119**(5): p. 554-7.

21. Dudley, M.E., et al., *Randomized selection design trial evaluating CD8+-enriched versus unselected tumor-infiltrating lymphocytes for adoptive cell therapy for patients with melanoma.* Journal of clinical oncology: official journal of the American Society of Clinical Oncology, 2013. **31**(17): p. 2152-2159.

22. Healy, G.B., et al., *Treatment of recurrent respiratory papillomatosis with human leukocyte interferon. Results of a multicenter randomized clinical trial.* N Engl J Med, 1988. **319**(7): p. 401-7.

23. Hatam, L.J., et al., *Immune suppression in premalignant respiratory papillomas: enriched functional CD4+Foxp3+ regulatory T cells and PD-1/PD-L1/L2 expression.* Clin Cancer Res, 2012. **18**(7): p. 1925-35.

24. Topalian, S.L., C.G. Drake, and D.M. Pardoll, *Immune checkpoint blockade: a common denominator approach to cancer therapy.* Cancer Cell, 2015. **27**(4): p. 450-61.

25. Stevanovic, S., et al., *Complete regression of metastatic cervical cancer after treatment with human papillomavirus-targeted tumor-infiltrating T cells.* J Clin Oncol, 2015. **33**(14): p. 1543-50.

26. Eisenhauer, E.A., et al., *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* Eur J Cancer, 2009. **45**(2): p. 228-47.

14 APPENDICES

14.1 APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale*	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

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14.2 APPENDIX B: VOICE HANDICAP INDEX-10

	Never 0	Almost never 1	Sometimes 2	Almost always 3	Always 4
My voice makes it difficult for people to hear me					
People have difficulty understanding me in a noisy room					
People as "what's wrong with your voice?"					
I feel as though I have to strain to produce voice					
My voice difficulties restrict personal and social life					
The clarity of my voice is unpredictable					
I feel left out of conversations because of my voice					
My voice problem causes me to lose income					
My voice problem upsets me					
My voice makes me feel handicapped					

Total Score:_____

As published in:

Journal of Voice. Arffa RE, Krishna P, Gartner-Schmidt J, Rosen CA. Normative values for the Voice Handicap Index-10. J Voice. 2012;26:462-465

Otolaryngology-Head and Neck Surgery: Kupfer R, Tatar E, Barry J, Allen C and Merati A. Anatomic derkay score is associated with voice handicap in laryngeal papillomatosis in adults. Otolaryngology-Head and Neck Surgery. In Press.

14.3 APPENDIX C: MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS

Immune-Related Adverse Events

Since inhibition of PD-L1 stimulates the immune system, immune-related AEs (irAEs) may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade):

Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring

Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4)

Grade 3 to 4: treat with high dose corticosteroids

14.3.1 Gastrointestinal irAEs

Gastrointestinal irAEs		
Severity of Diarrhea / Colitis (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (for example, loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Delay avelumab therapy Symptomatic treatment	If improves to Grade 1: Resume avelumab therapy If persists > 5 to 7 days or recur: 0.5 to 1.0 mg/kg/day methylprednisolone or equivalent When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy per protocol. If worsens or persists > 3 to 5 days with oral steroids: Treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 hrs; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Discontinue avelumab therapy per protocol 1.0 to 2.0 mg/kg/day methylprednisolone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade 1, then taper over at least 1 month If persists > 3 to 5 days, or recurs after improvement: Add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis

14.3.2 Dermatological AEs

Dermatological AEs		
Grade of Rash (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 to 2 Covering ≤ 30% body surface area	Symptomatic therapy (for example, antihistamines, topical steroids) Continue avelumab therapy	If persists > 1 to 2 weeks or recurs: Consider skin biopsy Delay avelumab therapy Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy If worsens: Treat as Grade 3 to 4
Grade 3 to 4 Covering > 30% body surface area; life threatening consequences	Delay or discontinue avelumab therapy Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent	If improves to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections Resume avelumab therapy

14.3.3 Pulmonary AEs

Pulmonary AEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 Radiographic changes only	Consider delay of avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-image at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4
Grade 2 Mild to moderate new symptoms	Delay avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent Consider bronchoscopy, lung biopsy	Re-image every 1 to 3 days If improves: When symptoms return to near Baseline, taper steroids over at least 1 month and then resume avelumab therapy and consider prophylactic antibiotics If not improving after 2 weeks or worsening: Treat as Grade 3 to 4
Grade 3 to 4 Severe new symptoms; New / worsening hypoxia; life-threatening	Discontinue avelumab therapy Hospitalize Pulmonary and Infectious Disease consults 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Baseline: Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)

14.3.4 Hepatic AEs

Hepatic AEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and / or total bilirubin > ULN to 1.5 x ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and / or total bilirubin > 1.5 to ≤ 3 x ULN	Delay avelumab therapy Increase frequency of monitoring to every 3 days	If returns to Baseline: Resume routine monitoring, resume avelumab therapy If elevations persist > 5 to 7 days or worsen: 0.5 to 1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or Baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy
Grade 3 to 4 AST or ALT > 5 x ULN and / or total bilirubin > 3 x ULN	Discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade 2: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines

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14.3.5 Cardiac AEs

Cardiac irAEs		
Myocarditis	**Management**	**Follow-up**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.* Methylprednisolone 1 to 2 mg/kg/day.	Once improving, taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A)
*Local guidelines, or eg. ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		

14.3.6 Endocrine AEs

Endocrine AEs		
Endocrine Disorder	**Management**	**Follow-up**
Asymptomatic TSH abnormality	Continue avelumab therapy If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include T4 at subsequent cycles as clinically indicated; consider endocrinology consult	
Symptomatic endocrinopathy	Evaluate endocrine function Consider pituitary scan Symptomatic with abnormal lab / pituitary scan: Delay avelumab therapy 1 to 2 mg/kg/day methylprednisolone IV or by mouth equivalent Initiate appropriate hormone therapy No abnormal lab / pituitary MRI scan but symptoms persist: Repeat labs in 1 to 3 weeks / MRI in 1 month	If improves (with or without hormone replacement): Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections Resume avelumab therapy Subjects with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (for example, severe dehydration, hypotension, shock out of proportion to current illness)	Delay or discontinue avelumab therapy Rule out sepsis Stress dose of IV steroids with mineralocorticoid activity IV fluids Consult endocrinologist If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy	

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14.4 APPENDIX D: DERKAY STAGING FOR RRP

STAGING ASSESSMENT FOR RECURRENT LARYNGEAL PAPILLOMATOSIS

PATIENT INITIALS:_____ DATE OF SURGERY_____ SURGEON_____
PATIENT ID #_____ INSTITUTION_____

1. How long since the last papilloma surgery? _____days, ____weeks, ____months,
   ____years,____ don't know,
   _____this is the child's first surgery
2. Counting today's surgery, how many papilloma surgeries in the past 12 months? _____
3. Describe the patient's voice today:
   normal__(0), abnormal__(1), aphonic__(2)
4. Describe the patient's stridor today:
   absent__(0), present with activity__(1), present at rest__(2)
5. Describe the urgency of today's intervention:
   scheduled__(0),elective__(1),urgent__(2),emergent(3)
6. Describe today's level of respiratory distress:
   none__(0), mild__(1), Mod__(2), severe__(3), extreme__(4)

Total score for questions 3-6=_____

FOR EACH SITE, SCORE AS: 0= NONE, 1= SURFACE LESION, 2=RAISED LESION, 3=BULKY LESION

LARYNX:
- Epiglottis
  - Lingual surface_____ Laryngeal surface_____
- Aryepiglottic folds: Right____ Left_____
- False vocal cords: Right____ Left_____
- True vocal cords: Right____ Left_____
- Arytenoids: Right_____ Left_____
- Anterior commissure_____
- Posterior commissure_____
- Subglottis _____

TRACHEA:
- Upper one-third_____
- Middle one-third_____
- Lower one-third_____
- Bronchi: Right____ Left_____
- Tracheotomy stoma_____

OTHER:
- Nose_____
- Palate_____
- Pharynx_____
- Esophagus_____
- Lungs_____
- Other_____

TOTAL SCORE ALL SITES: _____ TOTAL CLINICAL SCORE:_____

Fig. 1. Staging/severity scale.

The anatomic score will be used to determine response or progression-see section **5.2**